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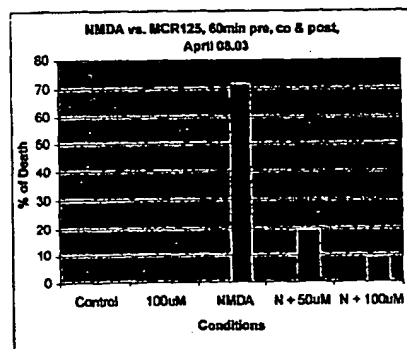
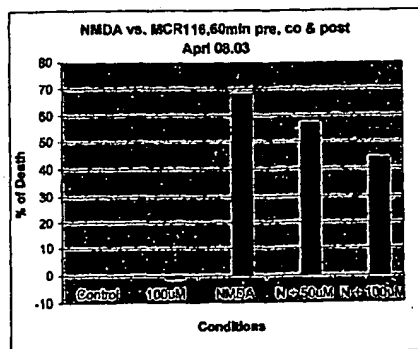
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(54) Title: **AMINO BENZOTHAZOLE COMPOUNDS WITH NOS INHIBITORY ACTIVITY**



(57) Abstract: The present invention provides novel amino benzothiazole compounds, compositions comprising these compounds and methods of using these compounds as neuroprotectants. In particular, the compounds described in the present invention are useful for treating stroke.

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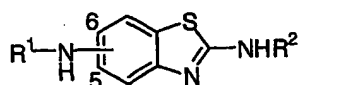
AMENDED CLAIMS

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Claim 1-37 related by claims 1-37.

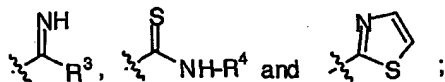
WE CLAIM:

1. A compound of Formula I, and pharmaceutically acceptable salts, hydrates, solvates and prodrugs thereof:

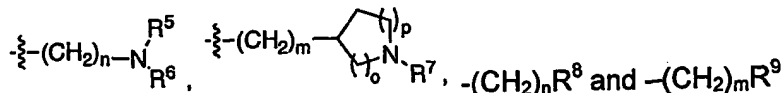


wherein

R¹ is selected from the group consisting of:



- 10 R² is selected from the group consisting of H,



R³ is selected from the group consisting of C₁₋₆alkyl, SC₁₋₆alkyl, thienyl and furanyl;

R⁴ is selected from the group consisting of H, C₁₋₆alkyl, Ph, C(O)Ph and

- 15 -C(O)C₁₋₆alkyl;

R⁵ and R⁶ are independently selected from the group consisting of H and C₁₋₆alkyl or together R⁵ and R⁶ and the nitrogen to which they are attached form a 3 to 7-membered azacarbocyclic ring wherein one of the carbon atoms in the ring may optionally be replaced with O, S, or NR⁷;

- 20 R⁷ is selected from the group consisting of H, C₁₋₆alkyl, Ph, Heteroaryl, CH₂Ph, and CH₂Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1-3 groups independently selected from the group consisting of C₁₋₄alkyl, halo, OH, OC₁₋₄alkyl, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro and cyano;

- 25 R⁸ is selected from the group consisting of H, OH, Ph, naphthyl and heteroaryl, with Ph, naphthyl and heteroaryl being optionally substituted with 1-3 groups independently selected from the group consisting of C₁₋₄alkyl, halo, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro, cyano, OH and OC₁₋₄alkyl;

R^9 is C_{3-7} cycloalkyl optionally substituted with 1-3 groups independently selected from the group consisting of C_{1-4} alkyl, halo, NH_2 , $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)(C_{1-4}alkyl)$, nitro, cyano, OH and $OC_{1-4}alkyl$ and one or two of the carbon atoms in C_{3-7} cycloalkyl may optionally be replaced with O or S;

5 n is 1-6;

m is 0-6;

o is 0-2;

p is 1-2; and

the group R^1NH- is attached to the 5- or 6-position of the aminobenzothiazole
10 ring, with the proviso that when R^2 is H then R^4 is not $C_{1-6}alkyl$.

2. The compound according to claim 1, wherein R^3 is selected from the group consisting of $C_{1-2}alkyl$, $SC_{1-4}alkyl$ and thienyl.

15 3. The compound according to claim 2, wherein R^3 is selected from the group consisting of $SC_{1-2}alkyl$ and thienyl.

4. The compound according to any one of claims 1-3, wherein R^4 is selected from the group consisting of H, $C_{1-4}alkyl$, Ph, $C(O)Ph$ and $-C(O)C_{1-4}alkyl$.
20

5. The compound according to claim 4, wherein R^4 is selected from the group consisting of H, and $C(O)Ph$.

25 6. The compound according to any one of claims 1-5, wherein R^5 and R^6 are independently selected from a group consisting of H and $C_{1-4}alkyl$ or together R^5 and R^6 and the nitrogen to which they are attached form a 4 to 6-membered azacarbocyclic ring wherein one of the carbon atoms in the ring may optionally be replaced with O, S, or NR^7 .

30

7. The compound according to claim 6, wherein R^5 and R^6 are independently selected from a group consisting of H and CH_3 or together R^5

and R⁶ and the nitrogen to which they are attached form a 5 to 6-membered azacarbocyclic ring.

8. The compound according to any one of claims 1-7, wherein R⁷ is selected from H, C₁₋₄alkyl, Ph, Heteroaryl, CH₂Ph, and CH₂Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1-2 groups independently selected from the group consisting of C₁₋₄alkyl, halo, OH, OC₁₋₄alkyl, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro and cyano.
9. The compound according to claim 8, wherein R⁷ is selected from H, C₁₋₄alkyl, Ph, Heteroaryl, CH₂Ph, and CH₂Heteroaryl, with Ph and Heteroaryl being optionally substituted with 1 group independently selected from the group consisting of C₁₋₄alkyl, halo, OH, OC₁₋₄alkyl, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro and cyano.
10. The compound according to claim 9, wherein R⁷ is selected from H, Ph, C₁₋₄alkyl and CH₂Ph, with Ph being optionally substituted with 1 groups independently selected from the group consisting of C₁₋₄alkyl, halo, OH, OC₁₋₄alkyl, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro and cyano.
11. The compound according to claim 10, wherein R⁷ is selected from H, C₁₋₂alkyl, Ph and CH₂Ph, with Ph being optionally substituted with 1 groups independently selected from the group consisting of methyl, halo, OH, methoxy, NH₂, NHMe, NMe₂ nitro and cyano.
12. The compound according to claim 11, wherein R⁷ is selected from methyl and CH₂Ph.
13. The compound according to any one of claims 1-12, wherein R⁸ is selected from the group consisting of H, OH, Ph and heteroaryl, with Ph and heteroaryl being optionally substituted with 1-2 groups independently selected

from the group consisting of C₁₋₄alkyl, halo, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro, cyano, OH and OC₁₋₄alkyl.

14. The compound according to claim 13, wherein R⁸ is selected from the group consisting of H, OH, Ph, and heteroaryl, with Ph and heteroaryl being optionally substituted with 1 group independently selected from the group consisting of C₁₋₄alkyl, halo, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro, cyano, OH and OC₁₋₄alkyl.

15. The compound according to any one of claims 13-14 wherein heteroaryl is a 5 or 6 membered aromatic ring.

16. The compound according to claim 15, wherein heteroaryl is selected from pyridyl, imidazolyl, thienyl and furanyl.

15

17. The compound according to any one of claims 1-16, wherein R⁹ is C₃₋₇cycloalkyl optionally substituted with 1-2 groups independently selected from the group consisting of C₁₋₄alkyl, halo, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro, cyano, OH and OC₁₋₄alkyl and wherein one of the carbon atoms in C₃₋₇cycloalkyl may optionally be replaced with O or S.

20

18. The compound according to claim 17, wherein R⁹ is C₅₋₇cycloalkyl optionally substituted with 1 group independently selected from the group consisting of C₁₋₄alkyl, halo, NH₂, NH(C₁₋₄alkyl), N(C₁₋₄alkyl)(C₁₋₄alkyl), nitro, cyano, OH and OC₁₋₄alkyl and wherein one of the carbon atoms in C₃₋₇cycloalkyl may optionally be replaced with O or S.

25

19. The compound according to claim 18, wherein R⁹ is C₅₋₇cycloalkyl wherein one of the carbon atoms in C₃₋₇cycloalkyl may optionally be replaced with O.

30

20. The compound according to claim 17, wherein R⁹ is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl and tetrahydrofuran.

5 21. The compound according to any one of claims 1-20, n is 1-4.

22. The compound according to claim 21, wherein n is 2.

23. The compound according to any one of claims 1-22, wherein m is 0-2.

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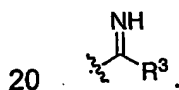
24. The compound according to claim 23, wherein m is 0.

25. The compound according to any one of claims 1-24, wherein both o and p are 1 (to provide a pyrrolidinyl ring).

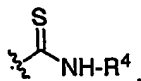
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26. The compound according to any one of claims 1-24, wherein both o and p are 2 (to provide a piperidinyl ring).

27. The compound according to any one of claims 1-26, wherein R¹ is



28. The compound according to any one of claims 1-26, wherein R¹ is



25 29. The compound according to claim 1 that is selected from the group consisting of:

N-(2-Amino-benzothiazol-6-yl)-2-methylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-ethylthiocarboximidamide;

N-(2-Amino-benzothiazol-6-yl)-2-propylthiocarboximidamide;

30 N-(2-Amino-benzothiazol-6-yl)-2-isopropylthiocarboximidamide;

- N-(2-Amino-benzothiazol-6-yl)-2-methylcarboximidamide;
N-(2-Amino-benzothiazol-6-yl)-2-thiophenecarboximidamide;
N-[2-(2-pyrrolidin-1-ylethylamino)-benzothiazol-6-yl]-2-thiophenecarboximidamide;
- 5 1-(2-Amino-benzothiazol-5-yl)-3-benzoyl-thiourea;
1-(2-Amino-benzothiazol-5-yl)-3-ethyl-thiourea;
N-(2-Amino-benzothiazol-5-yl)-thiophene-2-carboxamidine;
N5-Thiazol-2-yl-benzothiazole-2,5-diamine;
(2-Amino-benzothiazol-5-yl)-thiourea;
- 10 N-[2-(Tetrahydro-pyran-4-ylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-{2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-[2-(2-Pyridin-2-yl-ethylamino)-benzothiazol-6-yl]-thiophene-2-
- 15 carboxamidine;
N-[2-(1-Benzyl-piperidin-4-ylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-{2-[2-(3H-Imidazol-4-yl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
- 20 N-[2-(2-Morpholin-4-yl-ethylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-(2-Dimethylamino-ethylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-benzothiazol-6-yl]-thiophene-2-
- 25 carboxamidine;
N-{2-[2-(3-Chloro-phenyl)-ethylamino]-benzothiazol-6-yl}-thiophene-2-carboxamidine;
N-[2-(4-Hydroxy-butylamino)-benzothiazol-6-yl]-thiophene-2-carboxamidine;
N-[2-(3-Imidazol-1-yl-propylamino)-benzothiazol-6-yl]-thiophene-2-
- 30 carboxamidine;
N2-(1-Benzyl-piperidin-4-yl)-N6-thiazol-2-yl-benzothiazole-2,6-diamine;
1-Benzoyl-3-{2-[2-(4-bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiourea;

{2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl}-thiourea; and
1-[2-[2-(4-Bromo-phenyl)-ethylamino]-benzothiazol-6-yl]-2-ethyl-isothiourea.

5 30. A pharmaceutical composition comprising a compound according to any of claims 1-29 and a pharmaceutically acceptable carrier.

31. A method of treating, or reducing the risk of, a disease or condition which benefits from an inhibition of NOS activity comprising administering an effective amount of a compound according to any one of claims 1-29,
10 including those where R^2 is H and R^4 is C_{1-6} alkyl, to a cell or animal in need thereof.

32. A use of a compound according to any one of claims 1-29, including those where R^2 is H and R^4 is C_{1-6} alkyl, to treat, or reduce the risk of, a
15 disease or condition which benefits from an inhibition of NOS activity.

33. A use of a compound according to any one of claims 1-29, including those where R^2 is H and R^4 is C_{1-6} alkyl, to prepare a medicament to treat, or reduce the risk of, a disease or condition which benefits from an inhibition of
20 NOS activity.

34. The method according to claim 31, wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of migraine, inflammatory diseases including reversible obstructive
25 airway diseases (e.g., asthma and adult respiratory distress syndrome (ARDS)), stroke, neurological deficits associated with coronary artery bypass graft (CABG), acute and chronic pain, neuropathic pain, traumatic shock, reperfusion injury, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical
30 dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), epilepsy, anxiety, head trauma, morphine induced tolerance and

withdrawal symptoms, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic nephropathy.

35. The method according to claim 34, wherein the disease or condition
5 that may benefit from an inhibition of NOS activity is selected from the group consisting of stroke, reperfusion injury, neurodegeneration, head trauma, neurological deficits associated with CABG, migraine, neuropathic pain and chronic pain.

10 36. The use according to claim 32 or 33 wherein the disease or condition that may benefit from an inhibition of NOS activity is selected from the group consisting of migraine, inflammatory diseases including reversible obstructive airway diseases (e.g., asthma and adult respiratory distress syndrome (ARDS)), stroke, neurological deficits associated with coronary artery bypass
15 graft (CABG), acute and chronic pain, neuropathic pain, traumatic shock, reperfusion injury, multiple sclerosis, AIDS associated dementia, neurodegenerative diseases, neuron toxicity, Alzheimer's disease, chemical dependencies and addictions (e.g., dependencies on drugs, alcohol and nicotine), epilepsy, anxiety, head trauma, morphine induced tolerance and
20 withdrawal symptoms, acute spinal cord injury, Huntington's disease, Parkinson's disease, glaucoma, macular degeneration, diabetic nephropathy.

37. The use according to claim 36, wherein the disease or condition that
25 may benefit from an inhibition of NOS activity is selected from the group consisting of stroke, reperfusion injury, neurodegeneration, head trauma, neurological deficits associated with CABG, migraine, neuropathic pain and chronic pain.